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UNITED STATES PATENT & TRADEMARK OFFICE

Re: Application of: Ronald Brown MILLER, et al.

Serial No.: To Be Assigned

Filed: Simultaneously Herewith

For: **PHARMACEUTICAL FORMULATION**

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 200231

February 5, 2002

S i r:

Applicants respectfully request that the application filed herewith be amended as follows:

IN THE SPECIFICATION

On page 1, after the title of the invention, please **insert** the following paragraph:

- - This Application is a continuation of U.S. Application No. 09/043,321, filed July 27, 1998, hereby incorporated by reference. - -

Please insert the attached substitute abstract as page 11.

IN THE CLAIMS:

Please **amend** the claims as follows:

1. (Amended) A solid, oral, controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water at 25°C, said active ingredient dispersed in a matrix wherein the dosage form provides, as tested by the Ph. Eur. Basket method at 100 rpm 900 ml

aqueous buffer (pH 6.5) containing 0.05% w/w Polysorbate 80 at 37°C, an essentially zero order rate of release of the pharmaceutically active ingredient over a period of 8 hours, the amount of pharmaceutically active ingredient released over eight hours being in the range of 15% to 45%, and when tested in a group of at least five healthy humans the median tmax, based on blood sampling at half hourly intervals, is in the range of from about 2.5 to about 6 hours, and the ratio of mean Cmax to the mean plasma level at 24 hours is in the range of about 1.5 to about 3.5.

3. (Amended) A pharmaceutical dosage form according to claim 1, which has a W_{50} in the range from about 15 to about 35 hours when tested *in vivo* as set forth in claim 1.

4. (Amended) A pharmaceutical dosage form according to claim 1, wherein the matrix comprises a mixture of an hydrophobic fusible material having a melting point of greater than 40°C and a hydrophilic, organic, polymeric fusible wicking agent.

5. (Amended) A pharmaceutical dosage form according to claim 4, wherein the weight ratio of hydrophobic fusible material to hydrophilic , organic polymeric wicking agent in said mixture is in the range from about 8:1 to about 16:1.

6. (Amended) A pharmaceutical dosage form according to claim 1, in which the pharmaceutically active ingredient is morphine, a pharmaceutically acceptable salt thereof or mixtures thereof.

8. (Amended) A pharmaceutical dosage form according to claim 1, in the form of a tablet or a capsule containing multiparticulates.

9. (Amended) A process for preparing a dosage form according to claim 1 comprising:
(a) mechanically working in a high shear mixer a mixture of hydrophobic, fusible binder and a minor amount of an organic, fusible, polymeric material which in the finished dosage form is capable of functioning as a wicking agent at a speed and temperature at which the binder melts or softens and the mixture forms agglomerates;

(b) extruding the agglomerates whereby the extrudate is obtained as extruded pieces or an elongate extrudate is formed into pieces;

(c) continuing mechanically working the pieces in a high shear mixer; and

(d) continuing mechanically working with additional binder material at a temperature and speed at which the additional binder melts or softens.

10. (Amended) A process according to claim 9, wherein in stage (d) the additional binder melts or softens and binds with the particles.

11. (Amended) A solid, oral controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water at 25°C dispersed in a matrix, the dosage form being obtainable by a process comprising:

(a) mechanically working in a high shear mixer a mixture of hydrophobic, fusible binder and a minor amount of an organic, fusible, polymeric material which in the finished dosage form is capable of functioning as a wicking agent at a speed and temperature at which the binder melts or softens and the mixture forms agglomerates;

(b) extruding the agglomerates whereby the extrudate is obtained as extruded

pieces or an elongate extrudate is formed into pieces;

(c) continuing mechanically working the pieces in a high shear mixer; and

(d) continuing mechanically working with additional binder material at a temperature and speed at which the additional binder melts or softens.

Please **add** the following new claims as follows:

12. (New) A pharmaceutical dosage form according to claim 1, which has a W_{50} in the range from about 20 to about 30 hours when tested *in vivo* as set forth in claim 1.

13. (New) A pharmaceutical dosage form according to claim 1, in which the pharmaceutically active ingredient is morphine sulfate or morphine hydrochloride.

14. (New) A pharmaceutical dosage form according to claim 4, wherein the median t_{max} is in the range from about 2.5 to about 3.5 hours.

15. (New) A pharmaceutical dosage form according to claim 4, wherein the W_{50} is in a range from about 15 to about 35 hours.

16. (New) A pharmaceutical dosage form according to claim 4, wherein the W_{50} is in a range from about 20 to about 30 hours.

17. (New) A pharmaceutical dosage form according to claim 1, wherein the weight ratio of hydrophobic fusible material to hydrophilic organic polymeric wicking agent in said mixtures in the range from about 8:1 to about 16:1.

18. (New) A pharmaceutical dosage form according to claim 4, wherein the pharmaceutically active ingredient is morphine, a pharmaceutically acceptable salt thereof or mixture thereof.

19. (New) A pharmaceutical dosage form according to claim 4, wherein the pharmaceutically active ingredient is morphine sulfate or morphine hydrochloride.

20. (New) A pharmaceutical dosage form according to claim 5, wherein the pharmaceutically active ingredient is morphine, a pharmaceutically acceptable salt thereof or mixture thereof.

21. (New) A pharmaceutical dosage form according to claim 5, wherein the pharmaceutically active ingredient is morphine sulfate or morphine hydrochloride.

22. (New) A pharmaceutical dosage form according to claim 1, which is suitable for once a day dosing.

23. (New) A pharmaceutical dosage form according to claim 17, which is suitable for once a day dosing.

24. (New) A pharmaceutical dosage form according to claim 4, in the form of a tablet or capsule containing multiparticulates.

25. (New) A pharmaceutical dosage form according to claim 5, in the form of a tablet or capsule containing multiparticulates.

REMARKS

Claims 1-25 are pending in this application. Claims 1, 3, 4, 5, 6, 8, 9, 10 and 11 have been amended in order to reduce filing fees. New claims 12-25 have been added to further claim the instant invention. Support for the new claims is found throughout the application as filed.

A check in the amount of $830.00 is enclosed $90.00 of which is to cover claims in excess of 20. If it is determined that any additional fees are due, the Assistant Commissioner is hereby authorized to charge said fees to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly solicited

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: ______________________
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940

Marked-Up Amended Claim Set

1. (Amended) A solid, oral, controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water at 25°C, said active ingredient dispersed in a matrix [and] wherein the dosage form provides, as [when] tested by the Ph. Eur. Basket method at 100 rpm 900 ml aqueous buffer (pH 6.5) containing 0.05% w/w Polysorbate 80 at 37°C, an [has] essentially zero order rate of release of the pharmaceutically active ingredient over a period of 8 hours, the amount of pharmaceutically active ingredient released over eight hours being in the range of 15% to 45%, and when tested in a group of at least five healthy humans the median tmax, based on blood sampling at half hourly intervals, is in the range of from about 2.5 to about 6 hours, and the ratio of mean Cmax to the mean plasma level at 24 hours is in the range of about 1.5 to about 3.5.

3. (Amended) A pharmaceutical dosage form according to [any one of the preceding claims] claim 1, which has a W_{50} in the range from about 15 to about 35 hours [, preferably from 20 to 30 hours,] when tested in vivo as set forth in claim 1.

4. (Amended) A pharmaceutical dosage form according to claim 1, [2 or 3] wherein the matrix comprises a mixture of an hydrophobic fusible material having a melting point of greater than 40°C and a hydrophilic, organic, polymeric fusible wicking agent.

5. (Amended) A pharmaceutical dosage form according to [any one of] claim 4, wherein the weight ratio of hydrophobic fusible material to hydrophilic , organic polymeric wicking agent in said mixture is in the range from about 8:1 to about 16:1.

6. (Amended) A pharmaceutical dosage form according to [any one of the preceding claims] claim 1, in which the pharmaceutically active ingredient is morphine, a pharmaceutically

acceptable salt thereof or mixture thereof [of morphine, preferably morphine sulphate or morphine hydrochloride].

8. (Amended) A pharmaceutical dosage form according to [any one of the preceding claims] claim 1, in the form of a tablet or a capsule containing multiparticulates.

9. (Amended) A process for preparing a dosage form according to [any one of the preceding claims] claim 1 comprising:
(a) mechanically working in a high shear mixer a mixture of hydrophobic, fusible binder and a minor amount of an organic, fusible, polymeric material which in the finished dosage form is capable of functioning as a wicking agent at a speed and temperature at which the binder melts or softens and the mixture forms agglomerates;

(b) extruding the agglomerates whereby the extrudate is obtained as extruded pieces or an elongate extrudate is formed into pieces;

(c) continuing mechanically working the pieces in a high shear mixer; and

(d) continuing mechanically working with additional binder material at a temperature and speed at which the additional binder melts or softens.

10. (Amended) A process according to claim 9 [8], wherein in stage (d) the additional binder melts or softens and binds with the particles.

11. (Amended) A solid, oral controlled release pharmaceutical dosage form which comprises a pharmaceutically active ingredient having a solubility in water of greater than 1gm in 250ml water at 25°C dispersed in a matrix, the dosage form being obtainable by a process [as defined in claim 9 or 10] comprising:

(a) mechanically working in a high shear mixer a mixture of hydrophobic, fusible binder and a minor amount of an organic, fusible, polymeric material which in the finished dosage form is capable of functioning as a wicking agent at a speed and temperature at which the binder melts or softens and the mixture forms agglomerates;

(b) extruding the agglomerates whereby the extrudate is obtained as extruded pieces or an elongate extrudate is formed into pieces;

(c) continuing mechanically working the pieces in a high shear mixer; and

(d) continuing mechanically working with additional binder material at a temperature and speed at which the additional binder melts or softens.